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Wait and see ☆

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Abstract

Anticipatory behavior is aimed at goals that can be reached in the near future. Underlying this behavior are neurophysiological processes, which realize a setting of brain structures involved in the future perception, information processing and action. Anticipatory behavior is accompanied by slow brain potentials, which are generated in the cerebral cortex. They are known as the readiness potential (RP), the contingent negative variation (CNV) and the stimulus preceding negativity (SPN). The RP reflects the timing of a future voluntary movement. The CNV reflects the preparation of a signaled movement and the simultaneous anticipatory attention for the imperative stimulus. The SPN reflects partly the anticipatory attention for the upcoming stimulus. Although these slow potentials are generated in the cortex, the paper shows that a subcortical input from basal ganglia, and in the case of the RP also from the cerebellum, is a necessary condition for their emergence. Slow cortical potentials are the result of concerted activity in a number of cerebral networks, in which the thalamus forms a crucial node. It is suggested that the reticular nucleus of the thalamus plays a pivotal role in anticipatory attention.

Keywords: Readiness potential; Contingent negative variation; Stimulus preceding negativity; Anticipatory attention; Thalamocortical networks; Thalamic RN

1. Introduction

A subject, involved in a simple reaction time (RT) task, tries to respond as quickly as possible, once the imperative stimulus shows up. If a warning stimulus is presented prior to the occurrence of the imperative stimulus, mean RTs are shorter than in a simple RT task (Sanders and Wertheim, 1973). The warning stimulus provokes an alerting of the organism, which starts anticipatory processes resulting in a faster processing of either the sensory aspects, the central aspects or the motor aspects of the task. In the latter case we speak about motor preparation, in the former about anticipatory attention. The crucial element in both is their taking place *before* the presentation of the (imperative) stimulus. Listening to a spoken text would take much more time if we were to analyze what we heard word by word. The

☆ In memoriam: Some months after our symposium we received the sad news that our former co-worker and colleague Ernst Damen had suddenly died. Ernst was a very able investigator, whom we always will remember for his pioneer work on the SPN. We dedicate this paper to the memory of Ernst.

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use of rules belonging to a certain language makes it possible to anticipate the sequence of the words in the text we are listening at. Anticipatory attention helps in a faster processing of the words we hear. On the other side if we are talking, preparation of the movements needed to pronounce the words we want to say, allows a faster production of the words resulting in a fluent sentence or series of sentences. Anticipatory attention and motor preparation are manifestations of a top-down organization of behavior. The main topic of the present paper is the analysis of anticipatory attention, using recordings of the electro-encephalogram (EEG) during different tasks. Yet we will discuss motor preparation as an aside, since there is a formal similarity between slow potentials preceding the execution of a movement and those preceding the expected arrival of a stimulus. Our point of departure is that this formal similarity is a manifestation of a functional similarity between anticipatory processes in the sensory domain and in the motor domain. We will see that the functional match is based upon a comparable organization in the structures needed to perform anticipatory behavior.

After a description of the different anticipatory slow potentials we will see first that the origin of these potentials is cortical. Next we will show that for their emergence an input from subcortical structures is necessary. Then we will review the evidence for the existence of an attentional network in which both cortical and subcortical structures participate. Next we will discuss more specifically the role of the thalamus and its contribution to anticipatory attention. Finally we suggest that there is a slow wave reflecting anticipatory attention, for which a thalamic contribution is obligatory. We start our study with a description of the two best-known slow potentials in the EEG of both humans and monkeys: the readiness potential and the contingent negative variation.

2. Psychophysiological EEG recordings prior to a crucial event

Unilateral voluntary movements are preceded by a bilateral negative cortical potential, known as the Bereitschaftspotential or readiness potential (RP, Kornhuber and Deecke, 1965). With an onset of approximately 1200–1500 ms prior to the movement, this slow wave increases systematically in amplitude up to the onset of the movement. Its largest amplitudes are found over the motor cortex, contralateral to the finger movement side. There is a somatotopic organization in the distribution of this slow wave over the cortex. Besides the RP there is another slow wave, which also precedes movements, but now in response to a stimulus. This contingent negative variation (CNV) was recorded for the first time during the 1-s foreperiod of a warned reaction time task, i.e. between the presentation of the warning stimulus and the imperative stimulus (Walter et al., 1964). The CNV has also been coined 'expectancy wave', since the authors realized from the very beginning that their subjects were not only waiting to respond (Brunia et al., 1985), but also waiting for a stimulus to come (Brunia, 1999). The use of longer foreperiods (3–4 s) resulted in the discovery that at least two slow waves were hidden in the CNV: an early and a late wave. Their different distribution over the scalp suggested a difference in function (Loveless and Sanford, 1974). For a large part research became focused upon the late wave as an index for motor preparation. Larger late wave amplitudes preceded faster responses, and the paradoxical potential distribution with foot movements was equally present in RPs and CNV late waves (Brunia and Vingerhoets, 1980, 1981; for a summary see Rohrbaugh and Gaillard, 1983). Keeping the original interpretation of Walter et al. (1964) in mind, it has to be realized that subjects involved in a warned RT task are not only preparing a response: they are attending the future arrival of the imperative stimulus as well. Since there is a temporal overlap between these processes their electro-physiological reflection is necessarily confounded too, resulting in interpretation problems, which are not easy to overcome. Our solution for this problem was the time estimation paradigm, which we have used over the last ten years. In Section 3 we will show how anticipatory attention and motor preparation can be separated in time.

3. Anticipatory attention and motor preparation disentangled

In the time estimation paradigm, a warning stimulus has to be followed by a button press, after a fixed time interval of some seconds. Two or 3 s after the movement a knowledge of results (KR) stimulus is provided to inform the subject about whether s(he) responded in time, too early or too late. This was done by means of three visual symbols: a plus sign indicated that the subject was too late; a vertical line implied that the response was in the correct time window; and a horizontal line indicated that the response was too early (Damen and Brunia, 1987; Brunia and Damen, 1988). Experiments in which this paradigm is used result in two different slow waves: a movement preceding negativity (MPN) and a stimulus preceding negativity (SPN), depicted in Fig. 1. They have a different scalp distribution.

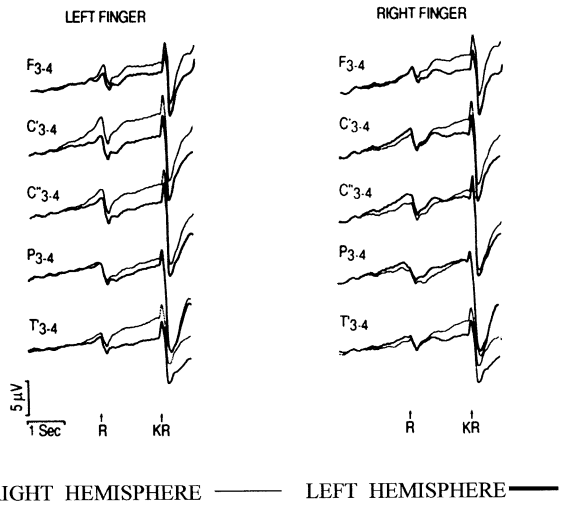

Fig. 1. In a time estimation task subjects had to press a button with either the right or the left hand in intervals of 20–22 s. Two seconds after each button press a knowledge of results (KR) stimulus was presented on a monitor. The KR stimulus indicated whether the preceding interval was too short, correct or too long. Preceding the movement an RP was recorded and prior to the KR stimulus an SPN was recorded. RP and SPN have a different potential distribution [adapted from Brunia (1988)].

The RP is larger over the hemisphere contralateral to a finger movement, and has its maximum amplitude over the motor cortex. The SPN has a right hemisphere preponderance, and shows an RP-like steeply increasing negativity over the parietal cortex and a sustained negativity over the frontal cortex. (Brunia and Damen, 1988). The question whether attention for the KR stimulus was the crucial factor in the emergence of the SPN, was answered by Chwilla and Brunia (1991), who investigated the SPN in three different conditions. In the first condition true feedback was given to the subjects, informing them correctly about their performance; in the second condition false feedback was given, using the same symbols but in a random order, and in the third condition no feedback was presented. The conditions were presented in blocks and only in the true feedback condition an SPN was recorded. Since the subjects knew that the feedback in the second condition was false, there was no need for them to attend the screen where the symbols were presented. We offered that as an explanation for the absence of the SPN in this condition. In another experiment Damen and Brunia (1994) investigated whether the SPN prior to an instruction stimulus is different from the one prior to a KR stimulus. After all, an instruction stimulus in a CNV paradigm indicates *that* a response should be produced, or *what* response should be produced, which is different from a KR stimulus, which indicates *how well* a past performance has been. The first is directed to the future, the second is directed to the past. The size and the potential distribution is indeed different: The SPN prior to the KR stimuli shows a clear right hemisphere preponderance and largest amplitudes over the parietal cortex, while the sustained negativity over the frontal electrodes was replicated too. In contrast, prior to the instruction stimuli only a slight bilateral negativity was found which was marginally significant. In a spatio-temporal dipole study, Böcker et al. (1994) suggested that a bilateral fronto-temporal dipole could explain most of the variance in the interval between movement and the presentation of the KR stimulus. It was hypothesized that the Insula Reili might be the location, which is activated, when a subject is

waiting for feedback about a past performance. Finally, Böcker et al. (1994) offered another explanation for the difference in shape of the SPN recorded over the frontal and parietal derivations by Brunia and Damen (1988). They suggested that the SPN would be a steady potential over all electrode positions, and that an overlap of this and a recurrence to baseline of the post-movement P3 would cause the increase in negativity over the parietal cortex. In other words this interpretation casts some doubt on a significant role of the parietal cortex in this very task. Another way of determining which areas in the brain are involved in waiting for KR and the use of KR to ameliorate the performance in the time estimation task is of course a PET study. Thus, Brunia et al. (2000) presented the first two conditions of the study of Chwilla and Brunia (1991) to their subjects, who were confronted with either true feedback of false feedback in blocks, two of each kind. Three areas in the right hemisphere were found to be activated: the prefrontal cortex (area 45), the Insula Reili, but now temporo-parietally, and the parietal cortex. So it seems that the performance of the time estimation task with KR about that performance, is accompanied by electrophysiological activity in a network in which these three areas play a major role. In the last section we will see that modality effects are present in the SPN too, suggesting that action in this hypothetical network can be initiated via different modalities.

Apart from the experiments in which an SPN was recorded prior to KR stimuli and prior to instruction stimuli, there are also a number of studies in which cues were used to give the subjects an instruction about what the response should be after the presentation of an imperative stimulus. Since the occurrence of these cues was also predictable in time, it could be expected that an SPN would show up here too. Indeed Gaillard and van Beijsterveld (1991) reported a symmetrical SPN prior to the cue, as did Van Boxtel and Brunia (1994). The SPN was small and bilaterally symmetrical. An SPN with a left hemisphere preponderance was reported by Ruchkin et al. (1986) prior to probe stimuli, which indicated to a subject whether a perceptual or conceptual task result did match with a probe stimulus presented at the end of a trial. Summarizing we conclude that an SPN was found prior to the onset of a KR stimulus, prior to the onset of a cue and prior to the onset of an instruction stimulus (for a review see Böcker and Van Boxtel, 1997). In all three cases the onset of the stimuli was predictable in time, and there was no confound with motor preparation. We consider this a necessary prerequisite to investigate anticipatory attention.

In so far the CNV is considered an anticipatory slow wave, it reflects for a large part motor preparation. In so far it reflects motor preparation, it can be compared to the RP. The CNV reflects also anticipatory attention for the instruction stimulus, but the electrophysiological contribution of the attentional processes is smaller than that of motor preparation. A pure SPN is easiest recorded in the time estimation task. We will use this as a basic tool for the investigation of anticipatory attention. As indicated in the introduction, we will now first examine what the sources are of these slow waves.

4. The electrophysiological sources of anticipatory slow waves

4.1. The electrophysiological sources are cortical

The electrophysiological sources of the RP have been studied more extensively than those of the CNV. In a large series of RP studies in monkeys, Sasaki and Gemba (see for a summary Sasaki and Gemba, 1991) have demonstrated a transcortical potential inversion in several (sensori) motor areas, i.e. in the primary motor cortex (MI), in line with earlier recordings of Arezzo and Vaughan (1980), but also in the premotor cortex (PMC), the supplementary motor area (SMA) and the primary somatosensory cortex (SI). The RP is supposed to stem from EPSPs present at the apical dendrites of the pyramidal cells in layer 5 of the cortex. Signaled movements stem by definition from brain areas activated *after* sensory organs are stimulated. Visual or auditory information is transmitted from posterior brain regions to (pre)frontal areas, which are involved in

the organization of motor acts (Rizolatti et al., 1998). This cortico-cortical activation of the cell columns in the motor cortex is, at least partially, responsible for the emergence of the slow potentials. To our knowledge there are no results available from slow wave studies in monkeys during anticipatory attention. There are, however, recordings of single unit activity in monkeys, which suggest that a similar anticipatory activity is present in the premotor cortex prior to stimulus presentation (Mauritz and Wise, 1986). We assume that an activation of the sensory cortex is present during anticipatory attention, comparable to that of the motor cortex during motor preparation.

4.2. RP and CNV need subcortical inputs for their emergence

While the cortical electrophysiological processes are considered necessary for the emergence of the RP and the CNV, they are not sufficient. Sasaki and Gemba (1991) have demonstrated that a lesion in the dentate nucleus, via which the cerebellar output is transmitted to the thalamus, hampers the emergence of the RP. This suggests that the dentato-thalamo-cortical pathway is a necessary factor for the bringing about of this slow wave. Investigations of the RP in Parkinsonian patients suggest further that the basal ganglia contribute to the development of the RP too (Deecke et al., 1977; Shibasaki et al., 1978, 1986; Dick et al., 1989; Jahanshahi et al., 1995; Praamstra et al., 1996). In other words the emergence of the RP might be realized via two separate thalamo-cortical channels, one via the cerebellum and the other via the basal ganglia. In the next paragraph we will discuss these circuits in more detail.

The CNV is also the result of a subcortical input, but now exclusively from the basal ganglia via the thalamo-cortical pathways. This suggestion is based upon a study of Ikeda et al. (1994), who investigated the CNV and RP in a patient with a lesion in the cerebellar dentate nucleus. They found a CNV late wave in a 2-s foreperiod over the frontal electrode positions, but no RP over the central electrode positions. Supporting evidence for a subcortical input stems from studies in both monkey (Rebert, 1977) and man (McCallum, 1988), reporting the presence of this slow potential in the mesencephalic reticular formation, and a positive slow wave with the same time course in the caudate nucleus. Since these structures project again to the thalamus, our understanding of the processes in the thalamo-cortical pathways and of the influences impinging thereupon is essential for an insight in electrophysiological processes accompanying anticipatory behavior.

So far it became plausible, that the emergence of RP and CNV late wave reflects anticipatory cortical activation, triggered via thalamo-cortical pathways. We have discussed above that the CNV late wave is a mixture of activity related to the preparation of a movement and of activity related to the anticipatory attention for the imperative stimulus. We consider it a plausible hypothesis that the SPN is equally generated by cortical neurons, which are activated via thalamo-cortical circuits. Since we interpret the SPN as a reflection of anticipatory attention, it is appropriate to discuss now first which subcortical structures are activated during anticipatory attention. Next we will see how these different structures participate in an attentional network, responsible for anticipatory activation.

5. Subcortical structures involved in attentive behavior

5.1. Superior colliculus and pulvinar

Hemianopic patients are able to look at or to point at a visual stimulus presented in their blind hemifield. This phenomenon, known as blindsight (Weiskrantz, 1986), could be explained by a still intact visual pathway from the retina, via the colliculus superior and the pulvinar to the parietal cortex. The colliculus superior is involved in the control of saccades to the invisible target, and the parietal cortex is involved in the control of the pointing movement to the invisible target. The dorsal stream in the visual system, classically considered responsible for spatial attention

(Mishkin et al., 1983), is probably an action-related system (Milner and Goodale, 1995). The investigation of attention to stimuli in the dorsal system is almost impossible without taking into account the responses to be given after stimulus presentation, be it looking, pointing, reaching or grasping (Milner and Goodale, 1995; Jeannerod, 1997). Here the anticipatory attention and the preparation of the movement are almost synonymous notions. Rizolatti's proposal of a premotor theory of attention suggests explicitly that attention to a spatially defined stimulus *is* the activation of a group of neurons involved in the response upon that stimulus (Rizolatti et al., 1994). There is sufficient evidence for the participation of the medial pulvinar in the anticipatory attention in the dorsal system.

The ventral stream, involved in the recognition of objects, consists of a series of cortico-cortical connections, but here again the thalamus is involved. The first important connection is the pathway from the lateral geniculate nucleus to the striate cortex (V1). Recurrent fibers stem from both the striate and extrastriate cortex. The second relevant thalamic nucleus is the pulvinar. Bender and Youakim (2001) describe three visual subdivisions in the visual pulvinar: an inferior, a lateral and a dorsomedial area. The inferior and the lateral pulvinar are driven from V1 and the extrastriate cortex. The inferior pulvinar receives also input from the superficial layers of the colliculus superior, which are directly connected to the retina (Benevento and Standage, 1983). The inferior pulvinar projects mainly to V2, V3, V3A and MT, while the lateral pulvinar projects to the more ventral areas of the inferotemporal cortex (Bender and Youakim, 2001). Theoretically, one would expect effects of anticipatory attention in the inferior and lateral pulvinar. The unit recordings in the monkey pulvinar and cortex, and the PET recordings of LaBerge and Buchsbaum (1990) were both aimed at demonstrating that. Bender and Youakim (2001) investigated whether attention modulated unit activity when their monkeys were to fixate a stimulus on a screen in front. In one of the conditions the animal waited for a spot of light to appear on the screen, looked at the spot until it dimmed and waited idly for a chance to begin a new trial. They found among other things a modulation in the firing of the pulvinar units, but approximately half of the units showed an increase and the other half a decrease in activity. The authors remark rightly that such a result never would have been found using averaging techniques like PET and fMRI. From the other side one wonders whether the task used by Bender and Youakim (2001) is more than fixating a light stimulus upon command. Such a behavior is certainly conditional for attention, but the attentional process follows after the eyes have successfully fixated the target. A spot of light is probably too simple a stimulus to really provoke an attentional process. That was not the case with the experiments of LaBerge and Buchsbaum (1990). These authors investigated the relation between selective attention and the pulvinar in a PET study. Subjects looked at a fixation point in the center of their visual field. A target letter O was presented in one hemifield, surrounded by similar but not identical letters, making the discovery of the O more difficult than when it was presented without these distracters. In case the O was recognized a button press was needed. In half of the trials a C or a Ø replaced the O: conditions in which no response was requested. The reasoning was that more attention was needed in the condition, where distractors surrounded the O. The pulvinar showed a significant glucose uptake during this more demanding task. Thus visual selective attention was indeed accompanied by an activation of the pulvinar. Given the type of task one would be inclined to suggest that the lateral and inferior pulvinar were involved, but the spatial resolution of the PET technique did not allow such a detailed conclusion.

5.2. Basal ganglia

In a PET study by Corbetta et al. (1991), normal subjects were asked to make discriminations between pairs of colored shapes. The members of each pair, being either the same or different in color, shape or speed, were presented one at a time under two different attention conditions: divided or focused. In the focused attention condition subjects were told what the relevant at-

tribute was, in the divided attention condition no advance information was given. This difference in behavior was reflected in the selective activation of the caudate and pallidal regions of the basal ganglia in the focused attention condition. In this condition subjects were certainly involved in an anticipatory attention task, but there is an important difference between the tasks used by LaBerge and Buchsbaum (1990) and Corbetta et al. (1991). Probably the anticipatory attention was less intense in the latter study, because (1) the discrimination of the target was not difficult; and (2) the time between the cue and target was 200 ms, which is not long enough to intensify anticipatory attention. LaBerge and Buchsbaum used a preparatory interval of 1400 ms, while in most of our SPN-studies intervals of 2000 ms are used. Since the results of the study of Corbetta et al. (1991) suggest that the basal ganglia are also involved in anticipatory selective attention, we will first examine some of the anatomical relations, relevant for our understanding of that behavior.

Almost all cortical areas project to the striatum (caudate nucleus and putamen), which funnels information via the pallidum and thalamus back to the frontal cortex (Fig. 2). Within these connections, Alexander et al. (1986) distinguished five different circuits, which are organized in parallel, but remain segregated from each other, both structurally and functionally (see also Alexander and Chrutcher, 1990). The *motor circuit* is aimed at the precentral motor fields and is involved in motor preparation and execution of movements. The *oculomotor circuit* is connected to the frontal and supplementary eye fields and is involved in orienting behavior. The *limbic circuit* is aimed at the anterior cingulate and medial orbitofrontal cortex, and is related to motivational aspects of behavior. Two *prefrontal circuits* are focused on the dorsolateral prefrontal and lateral orbitofrontal cortex. They are involved in cognitive behavior. The information processed by these circuits is different, but the general organization of each circuit seems to be the same: it probably consists of a large array of modules, which run relevant information in parallel (Houk, 1995).

Within each circuit the basal ganglia influence

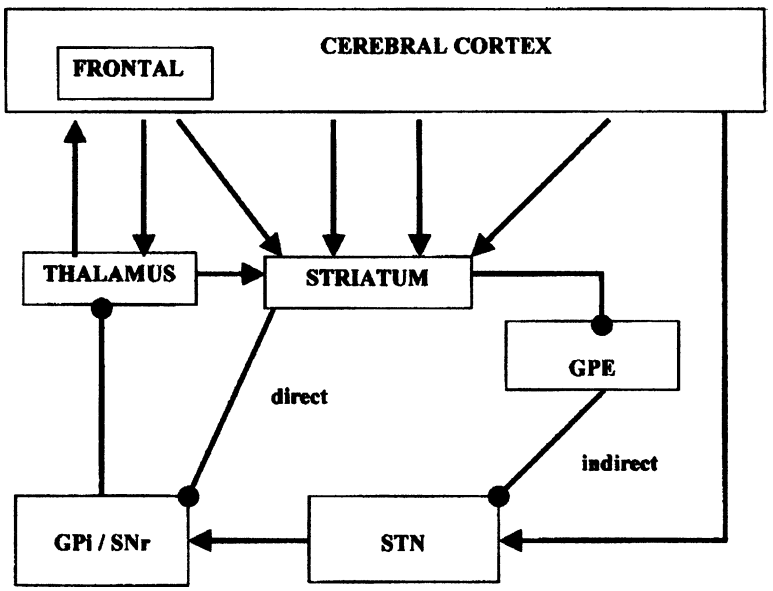

Fig. 2. Connections between thalamus, basal ganglia and cortex. Globus pallidum interna (Gpi) and substantia nigra pars reticulata (SNr) are under a direct inhibitory control and an indirect excitatory control from the striatum. The subthalamic nucleus (STN) is under an inhibitory control of the external pallidum (GPE) and an excitatory control of the cortex cerebri. Excitatory: →; Inhibitory: → [modified after DeLong (1990)].

the different thalamic nuclei (N. ventralis anterior, N. ventralis lateralis and N. dorsomedialis) via two different pathways, a direct and an indirect one. The balance between the two determines the end result at the thalamic level. At rest the striatal spiny GABA-ergic neurons show nearly any activity while the pallidal neurons are tonically active. Thus at rest the thalamic neurons are inhibited via the direct connection from the globus pallidus internus (GPi) and the substantia nigra pars reticularis (SNr). The subthalamic nucleus is inhibited by the external pallidum (Gpe) via the indirect connection. Excitation of the striatum from the cortex results in an increase in activity of the spiny neurons. This has two effects: (1) via the direct route the inhibitory neurons of the Gpi/SNr are inhibited, which results in a disinhibition of the thalamic neurons; and (2) via the indirect route the GPe is inhibited, which results in a disinhibition of the STN, and via that to an inhibitory effect upon the thalamic neurons. The balance between the two determines what will happen in a given situation. Fig. 3 shows how the inhibition upon the thalamus can be interrupted by a burst of spiny neurons in the striatum (Chevalier and Deniau, 1990) and how this results in a short burst of thalamic neurons. Houk and Wise (1993) postulated that the rebound burst might initiate a positive feedback in the corticothalamic loop, causing a sustained firing of the frontal and thalamic neurons, which might be (part of) a working memory circuit. Schultz et al. (1995a,b) have pointed to the anticipatory firing of striatum spiny neurons in monkeys, not only during the preparation of a response, but also during the anticipation of instruction stimuli, trigger stimuli and reward. We suggest that effects of this anticipatory activity in the striatum are reflected at the cortical level in the SPN, which we have recorded in man. It is interesting that Fig. 2.4 of Schultz et al. (1995a) concerns conditions under which anticipatory firing of striatal units

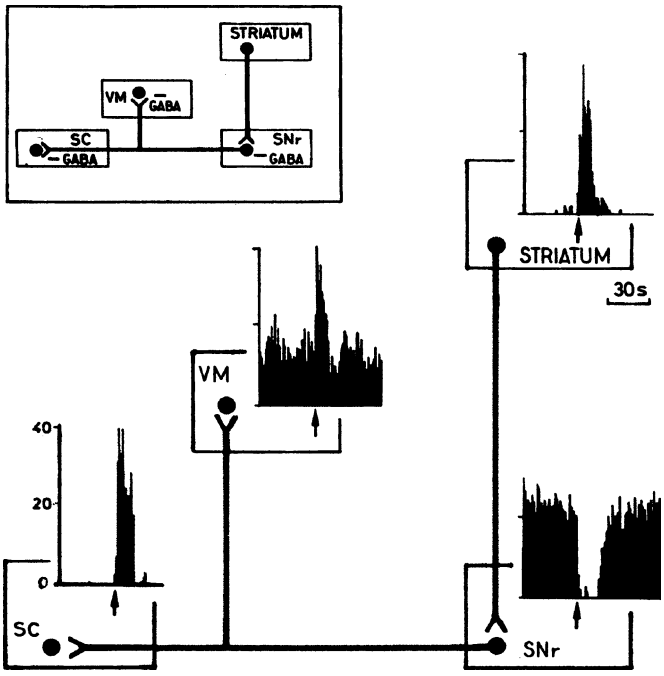

Fig. 3. Organization of the striato-nigrofugal pathways to the ventromedial thalamic nucleus (VM) and the superior colliculus (SC). The insert shows the two serial GABA-ergic inhibitory links. Spike frequency histograms (spikes per second) illustrate the sequences of electrophysiological events underlying the disinhibitory influence of the striatum. The striatal spike discharge, induced by a local application of glutamate is followed by a silencing of the tonically active nigral neurons (SNr), resulting in a discharge of collicular and thalamic neurons, which are freed from the potent nigral inhibition (Chevalier and Deniau, 1990).

has been found, and that under very similar conditions we have recorded different types of SPN. A behavioral expectation of a future event has to be based upon some knowledge about that event. That knowledge is stored temporarily in the working memory created for the duration of an experiment either by instruction or by recent experience (learning). The basal ganglia are involved in the detection and analysis of the context in which the behavior takes place (Schultz et al., 1995a). The fact that basal ganglia and thalamus are activated in anticipatory attentive behavior suggests that this behavior is based upon activity in a network, rather than being directed from just one (cortical) area. In Section 6 we will review several proposals about attentive networks.

6. Attention is based upon a specific network

The analysis of a syndrome known as hemineglect in macaque monkeys, has led Mesulam (1983) to suggest that the dorsal portion of the inferior parietal lobe (area PG) plays a crucial role in attentional behavior. In this area neurons have been found to increase their firing rate preceding reaching toward a desirable object, grasping, the onset of eye movements and perceiving a stimulus in the periphery of the visual field without making a saccade towards it. Milner and Goodale (1995) suggested that within the intraparietal sulcus different areas are involved in these functions. Mesulam (1981) classified the different areas with afferent connections to PG in four categories: 'sensory association', 'limbic', 'reticular' and 'motor'. Polymodal sensory cortex and pulvinar medialis belong to the first category, cingulate gyrus and basal forebrain contribute to the limbic input and brainstem raphe nuclei, locus coeruleus and the intralaminar thalamus form the reticular input to area PG. The output from PG would be directed to frontal eye fields and superior colliculus. Mesulam suggested that convergence of limbic with sensory input might underlie the finding that animals only responded upon stimuli, which were of motivational value to them. The reticular input might contribute to the arousal level, needed as a basic state for attentional behavior, whereas the motor part would be responsible for exploratory and orienting behavior. Mesulam (1983) explicitly states that his paper is restricted to the distribution of sensory attention within extra-personal space. His notion that attentive behavior is based upon electrophysiological activity in a network of different brain areas, is in line with clinical evidence that hemi-neglect in human beings may stem from lesions in large number of brain areas (see, e.g. Mesulam, 1981; Heilman et al., 1993). The crucial area in Mesulam's theory is area PG, to which information from different brain areas is funneled, before it is put through to the motor areas in the frontal cortex. It is obvious that different aspects of perceived objects can be put together (e.g. attractiveness, form and color), but what the essence is of the attentive process in Mesulam's theory remains unsolved. This is probably caused by the fact that there is no clear distinction between a perceptual data processing system, which informs us, e.g. about our environment, and an attentive system, which has a selective intensifying influence upon some of the nodes of the data processing network, in order to optimize its functioning.

The idea that the attention system is separate from a perceptual data processing system is present in the work of Posner and Peterson (1990). They distinguish an anterior attention system and a posterior attention system. The posterior system involves the dorsal visual pathway from the primary visual cortex V1 into the parietal cortex, the superior colliculus and the pulvinar, in other words all structures that were also crucial in Mesulam's hypothetical network (Mesulam, 1981). Posner (1995) is much more explicit in what the different areas involved in the posterior *orienting network* might be doing during shifts of attention. He hypothesized that the parietal cortex disengages attention from the area where attention was paid to before, after which the colliculus superior can move attention to a new area, while the pulvinar is involved in restricting input to the indexed area. Thus the pulvinar contributes to the selective process, while the very selection is realized at the cortical level. Anticipatory atten-

tion starts after the orienting system has engaged a new target, e.g. the location where a crucial stimulus will show up. We suggest that its ongoing activity is reflected in the SPN recorded prior to the presentation of that stimulus. In the anterior *executive network* the cingulate gyrus seems to play a major role. Vogt et al. (1992) suggested that the posterior part of the cingulate gyrus is involved in evaluative processes and the anterior part in task execution. The local anatomy shows columns of cells with alternating connections to the prefrontal cortex and to the posterior parietal cortex (Goldman-Rakic, 1988), suggesting an intermediate role for the anterior cingulate gyrus between these association areas. Moreover, the anterior cingulate gyrus gets an input from the amygdala (LeDoux, 1996), allowing directing attention to emotionally relevant stimuli. Apart from the indirect connection between both prefrontal and parietal cortical areas, Goldman-Rakic and Porrino (1985) found also a direct connection with the posterior parietal cortex, together with terminals in the mediodorsal nucleus of the thalamus and in the pulvinar. The first might play a role in the executive network, while the latter is part of an attentional circuit.

More or less the same areas play a role in the attention system, proposed by LaBerge (1995; also this volume). For him the prefrontal cortex, the parietal cortex and the pulvinar are the major components of a triangular network involved in attentive behavior. Again there is a clear separation between an information processing system and a system that selectively is directed upon an improvement of perceptive processes. Directing attention is an affair of the prefrontal cortex, which is connected to the pulvinar. The result of the attentive processing becomes manifest in the parietal cortex, which is interpreted as an expression of attention. The way in which a better stimulus-to-noise ratio is reached is a consequence of the functioning of the circuitry between pulvinar and parietal cortex, in which the reticular nucleus (RN) plays a major role. LaBerge et al. (1992) concluded from a simulation study that both enhancement of activity in a specific set of neurons and decrease in noise in neighboring neurons, might be the explanation for the attention effect. The enhancement producing circuits might be the thalamo-cortical loop, which, in visual perception, comes down to the pulvinar with its connections with a large number of visual cortical areas. The way in which the excitatory and inhibitory synapses are distributed within the circuit between thalamus, RN and cortical columns, suggests that it is indeed able to produce a focal enhancement of activity in a set of cortical columns. The amplifier function is not possible without the contribution of the RN. We will see next that not everybody is convinced of the importance of the thalamic circuitry for selective or anticipatory attention.

An important point in Mesulam's analysis is the fact that the sensory input to area PG stems from higher order polymodal sensory areas and the medial pulvinar. After arrival in a primary sensory area information is put through unimodal association areas to polymodal association areas before area PG is reached. Most electrophysiological studies of attention in both monkey and man use within-modality paradigms. In other words attentional processes are investigated in unimodal association areas at the utmost. In his chapter on the physiological basis of selective attention, Woods (1990) has pointed to the differing attention-related ERPs found in different modalities. Also the distribution of these attention-related ERPs is modality-specific. Auditory effects are largest over the fronto-central derivations, somatosensory effects are largest centrally and visual effects are largest over the parietal and occipital lobes. So, whatever the mechanism for attention to be active in one modality only, there has to be a way back from the 'higher' polymodal nodes in the attentional network to the unimodal sensory areas, and perhaps even back to the primary projection areas. There are indeed recurrent pathways from higher-order sensory areas to lower-order sensory pathways, allowing a top-down control of information processing in the latter. Woods (1990) points to the fact that attentional modulation of firing of cells in the primary cortices takes place well *after* the arrival of the thalamo-cortical volley, which suggests to him that the selective attention is an affair of recurrent cortical pathways rather than of thalamo-cortical

pathways. Next he argues that attentional modulation is more prominent in the upper three layers of the sensory cortex, which receive the cortico-cortical fibers, whereas the thalamic input enters in layer 4. In other words, to be modulated by attention the thalamo-cortical input arrives at the wrong time and in the wrong place. The tacit implication of his suggestion is of course that the thalamus is a relay station, which has to be passed to reach the cortex. Once the thalamo-cortical fibers have entered cortical layer 4 and once this input has been transmitted to the upper cortical layers in the cell column, the higher processes could start, so it seems. The many cortico-thalamic fibers are not taken into consideration, though, and they might very well be of importance for attentive behavior. We will discuss that next, but like to make a caveat here. In a recent paper Lamme and Roelfsema (2000) considered the feedforward sweep from V1 to the following visual areas important for pre-attentive vision. The recurrent cortico-cortical fibers from higher to lower visual areas would be crucial for attentive analysis. Thus, although the present paper stresses the importance of thalamo-cortical connections to realize attentive behavior, it seems that we have to accept that attention can be brought about by cortico-cortical and by thalamo-cortical connections. We will now discuss the consequences of the abundant cortico-thalamic fibers in relation to attention.

7. Cortico-thalamic control: an attentional device

The large amount of cortico-thalamic connections suggests the possibility of some top-down influence upon the data processing within the thalamic nuclei. The actual control upon ongoing behavior determines which stream of information has priority: bottom-up or top-down. An important condition for anticipatory behavior is the availability of knowledge about events to happen in the near future. We have seen above that the basal ganglia play a role in context detection and in the formation of a working memory. In this working memory instructions about a future behavior are kept in order to be implemented in actual behavior. In the executive control of behavior the (dorsolateral) prefrontal cortex seems to play a major role. Preparation is not only the setting of the necessary motor structures, but also of the sensory areas, where the to be expected information will become available. Such an organization of behavior might be realized via cortico-cortical connections from the prefrontal cortex, but also via descending pathways from the cortex via the basal ganglia and the thalamus back to the cortex or by cortico-thalamo-cortical connections. The latter might participate in the top-down control of information processing in the thalamus (Deschênes et al., 1998). Since the thalamus is part of the circuitry in two of these three connections, it is time to give its anatomy a closer inspection.

8. The thalamus: an important node between periphery and cortex

The dorsal thalamus, to which we refer as ‘the thalamus’, consists of a number of nuclei, which are connected to different parts of the cerebral cortex. Probably no part of the cortex is devoid of thalamic input. Approximately 30% of the afferent sensory and motor fibers to the cortex stem from one of the thalamic nuclei (Creutzfeldt, 1995). The whole set of nuclei is covered by a thin sheet of cells, known as the RN, which forms, together with the perigeniculate nucleus and the zona incerta, the ventral thalamus. The RN is the only nucleus that sends no afferents to the cortex. It receives excitatory collaterals from both ascending thalamo-cortical fibers and descending cortico-thalamic fibers. The RN is divided in a number of sectors, which are related to differing thalamo-cortical pathways. Thus there are, e.g. separate sectors for visual, auditory, somatosensory and motor functions, while others are controlling the anterior and mediodorsal nucleus (Guillery et al., 1998). RN cells have a GABA-ergic inhibitory control over the underlying thalamic ‘relay’ nuclei (see Fig. 4). There exists also an extensive inhibitory communication with other cells in the RN. The local inhibitory influence upon the thalamic relay nuclei might play an

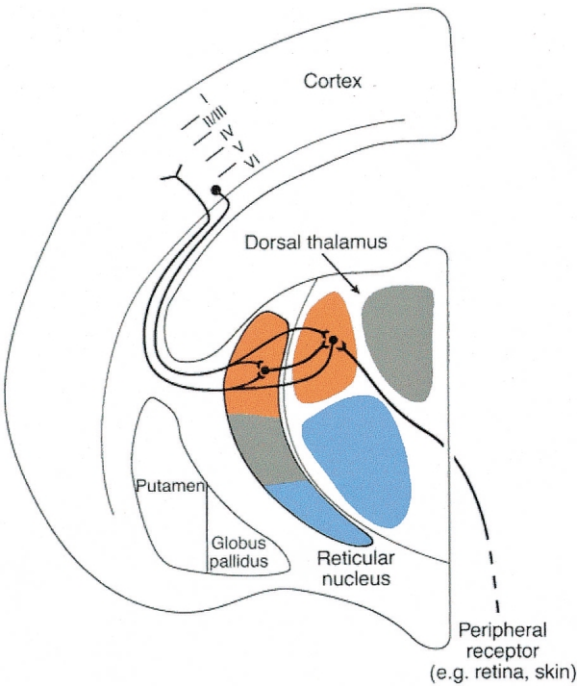

Fig. 4. Different sectors of the thalamic RN inhibit differing thalamic nuclei. Both ascending and descending fibers give collaterals to the RN [from Mitrofanis and Guillery (1993)].

important role in selective attention and motor preparation.

In a recent description of the thalamo-cortical relations, Guillery et al. (1998) point to the different way in which *first order* nuclei and *higher order* nuclei are interconnected to the cortex. The first order (FO) neurons are driven by the primary afferents from the sensory organs; the higher order (HO) neurons are driven from the cortex. Ascending afferents (e.g. from the retina) end near the soma of the FO neurons (e.g. in the lateral geniculate nucleus), the axons of which pierce the RN under way to cortical layers 4 and 3. From here fibers ascend to layer 2, from which layers 5 and 6 are reached. Fibers from layer 6 return partly to layer 4, thus closing this local excitatory minicircuit, while others return from layer 6 to the dendrites of the sensory nucleus where the original ascending fibers did come from. The major drive for the HO neurons stems from neurons in cortical layer 5. Their axons also end near the soma of the HO neurons. Layer 6 axons end, like those from the FO cells, on the dendrites of the HO neurons, where they have a modulatory influence. Thus the drive is in the FO neurons bottom-up, and in the HO neurons top-down. The driving axons have no collaterals to the RN, in contrast to the modulatory ascending fibers from both FO and HO cells and the modulatory descending fibers from neurons in layer 6. The ascending fibers end near the soma of the RN cells, and the descending fibers end at more distal dendrites (see Fig. 5), suggesting a possible difference in power to activate the inhibition.

Guillery et al. (1998) clarify that the circuitry within the different RN sectors is different for each modality. This suggests to these authors that it is probably too early for clear statements about the role of the RN in attention. Yet, they stress that the topographic order in its connections and its consequent capacity to focus on limited parts of the environment or of other brain parts, is playing a key role in a defined function, which might very well be attention (among others). Over the last decennia several suggestions have been presented concerning a possible role of the RN in attention: a topic that we will discuss next.

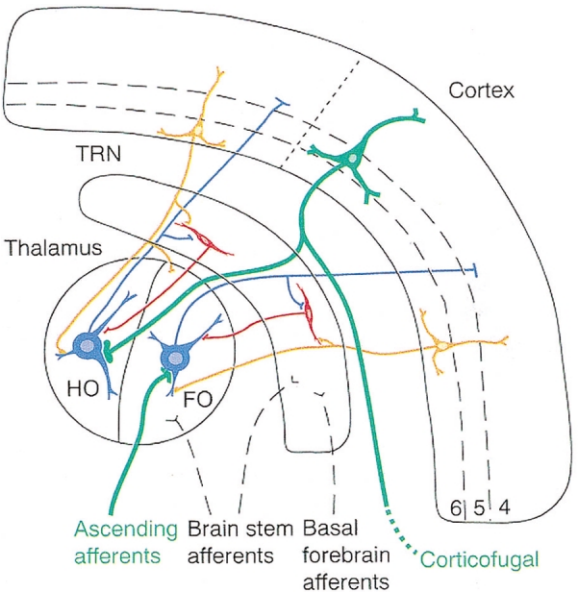

Fig. 5. Relationship between first order (FO) and higher order (HO) thalamic nuclei, the RN and the cortical projection areas. For details see text (from Guillery et al. (1998)].

9. Is the RN involved in anticipatory attention?

In one way or another attention has to do with a better perceiving of the stimuli one is (going to be) confronted with. Therefore, the basic mechanism must be some improvement of the signal-to-noise ratio in the information one is aimed at. So either the effect of the crucial stimuli has to be enhanced or the noise has to be suppressed. This is a constant element in the proposed mechanisms of attention.

An example of a theory in which the inhibition of irrelevant information is crucial, is the proposal by Skinner and Yingling (1977), and Yingling and Skinner (1977). These authors hypothesized that selective (*intermodal*) attention might be realized by a frontal control over the RN via the inferior thalamic peduncle. Excitation of the inhibitory neurons in the RN would lead to a closing of the thalamo-cortical gates. Absence of this excitation would leave the attended gate open, so that output from the crucial thalamic nucleus could reach the cortex. It should be noted, though, that the input from the prefrontal cortex arrives at the rostral part of the RN, while the channels involved in selective attention are localized in the posterior part of the thalamus. In other words a connection between the anterior part and the posterior part of the RN is needed, to provide a pathway via which selective attention could be realized. In the anatomical descriptions of the thalamo-cortical circuitry we have seen that each thalamic nucleus projects to a circumscribed part of the cortex, from where it receives returning descending fibers. Collaterals of the ascending and descending fibers enter those parts of the RN that control the specific thalamic nucleus in question. These connections are of no help for the model of attention, we are discussing. The model would be saved, though, if fibers from the anterior NR would innervate RN cells in the posterior part. Excitation from the prefrontal cortex would then lead to disinhibition of RN neurons in the posterior part. Selection in the disinhibition would be responsible for an open gate. However, at the moment there is insufficient anatomical evidence for such a circuitry.

Recently Van der Werf et al. (submitted) described four different clusters of cells in the thalamic intralaminar and midline nuclei, three of which produce an important input to the dorsal striatum. The different clusters are connected to various cortical areas. They receive specific sets of afferent fibers and send efferent fibers to specific parts of cortex and striatum. The targets of the thalamo-cortical and thalamo-striatal projections are interconnected via cortico-striatal projections (Groenewegen and Berendse, 1994). 'Through distinct sets of inputs to individual midline or intralaminar nuclei, these nuclei are in a position to interact selectively with particular functionally segregated basal ganglia-thalamo-cortical circuits' (Groenewegen and Berendse, 1994). In this case the RN might be involved, since part of the circuit is thalamo-cortical, but then, admittedly, only in an indirect way. This holds also for the prefrontal–cortical connections. Since descending cortico-thalamic fibers from each of the cortical areas send collaterals to the RN, a local inhibitory influence of the RN could be the consequence of the activation of the cortico-thalamic pathway.

Another approach stems from Crick (1984). He took as starting point the fact that thalamic neurons have two distinct firing modes. If such neurons are near their resting potentials they respond upon an injected current with a firing rate between 25 and 100 spikes/s. This is called the 'tonic mode'. If the negative potential of the cell membrane is increased, thus if the cell is hyperpolarized, e.g. by an inhibitory influence of an RN neuron, the cell is in the 'burst mode'. It responds upon an injected current with a burst of 300 spikes/s. Crick (1984) suggested that the first spikes of the train could be used to set up a temporary network of neurons, that would be able to realize the conjunction between features of an attended object, in line with suggestions of Treisman and Gelade (1980). At first sight there is a problem here too. If cells are in the burst mode they are considered not to be able to process any information, which does not seem compatible with any kind of attention. Yet Guillery et al. (1998) suggest that even in the burst mode thalamo-cortical cells can respond upon sensory stimuli. The cells are primed to changes in input,

which can be the cause of a switch to the tonic mode. Only the latter seems to be compatible with ongoing information processing, and thus with attention.

In Posner's proposal of the posterior attention network (Posner, 1995) the pulvinar has the well-defined function to keep selection going. How that is brought about remains unclear, though, at least in Posner's work. LaBerge's hypothesis is well suited to explain the mechanism via which the selection might be realized. A problem not addressed though, is the modality of the stimuli one is aimed at. The pulvinar is considered in the different theories discussed as visual association area. Yet there are a number of neurons in the pulvinar that respond upon auditory stimuli, both in cat and monkey (Margariños-Ascone et al., 1988). So the question is whether the proposed mechanisms hold for the auditory and somatosensory mode too. This could mean that the pulvinar might be involved, but also other association nuclei in these modalities, e.g. the dorsal part of the medial geniculate nucleus in the auditory mode, and the medial division of the posterior group in the somatosensory modality (Guillery et al., 1998). Frith and Friston (1996) found in a PET study, in which subjects had to attend to tones, an increase in activity in the right thalamus, but more anterior than the pulvinar. This suggests that it is implausible that the medial geniculate nucleus is the activated area, which on its turn suggests a difference with the visual system. From the other side, although the location of the increased activity remains puzzling, at least a thalamic participation to an attentive process in the auditory modality has been found here. Whatever the solution of this unclarity, the intriguing point remains that for each thalamic nucleus there is a dedicated sector of the RN, which might be involved in the realization of a better stimulus-to-noise ratio. For some time there is behavioral evidence for that, as we will see next.

Recently Weese et al. (1999) investigated, to our knowledge for the first time, the influence of the RN upon attentive behavior in rats. The task was designed in such a way that covert attention could be distinguished from overt orienting movements. From experiments in humans we know that cueing attention to a spatial location decreases RT upon presentation of the stimulus (Posner, 1995). This beneficial effect is also present in rats (Weese et al., 1999), which is not that surprising if one realizes that the so-called Posner paradigm stems from the work of Ingle (1975) in frogs. It only suggests that there exists a commonality in the organization of orienting behavior in different species. Weese et al. (1999) made a unilateral lesion in the visual sector of the RN with a chemical infusion of the neurotoxin ibotenic acid. This results in a loss of the beneficial effect of contralateral cues preceding contralateral targets and not in a change of the cost of a contralateral cue and an ipsilateral target. The benefit of a valid cue upon RT to a visual target is found over species and underlines the important contribution of the RN to spatial attention.

10. Does the emergence of the SPN depend upon a thalamic input?

We have seen above that for the emergence of both the CNV and the RP a thalamo-cortical input is necessary. The paradigm used for the distinction of potentials related to anticipatory attention and motor preparation has demonstrated the existence of a slow wave (the SPN) reflecting anticipatory attention. We assumed that a thalamo-cortical input is necessary here too. There is direct evidence that the pulvinar is involved in attentive behavior. Administration of GABA-ergic components into the pulvinar modifies the shift of attention in monkeys in the contralateral hemifield. Rafal and Posner (1987) described a similar result in patients with thalamic lesions. Attention for visual stimuli in the study of LaBerge and Buchsbaum (1990) resulted in an increase in activation of the pulvinar. We assume that the same holds for the visual stimuli in our EEG experiments. In our PET study we found activation in the lateral prefrontal cortex, the parietal cortex and the posterior operculum, probably participating in a network, responsible for the timely execution of the movement with support of visual KR stimuli. Apart from the

'higher' processes in the performance of our task, we expected an activation of the specific unimodal visual (association) cortex. They were not present in the PET study, because the same visual symbols were used in the experimental and control condition. In a not yet published study we found larger SPN amplitudes over the occipital cortex, when a visual KR stimulus was presented than when an auditory KR stimulus was presented, while over the frontal electrodes the picture was reversed: SPN amplitudes were larger prior to an auditory KR stimulus than prior to a visual KR stimulus. In other words, the SPN in the time estimation task seems to reflect activity in a fronto-temporo-parietal network, the activity of which can be initiated from different sensory areas. We consider the sustained negativity over the frontal cortex an index of two processes: (1) the ongoing control over the timely execution of the movements for which the KR information has to be implemented in the next trial; and (2) the ongoing control over the attentive processes in the posterior cortex. The systematic increase in amplitude over the parietal cortex is interpreted as an index of anticipatory attention, a process in which the thalamus plays a crucial role. For visual attention it seems likely that the pulvinar is the crucial node, for other modalities different nuclei might be involved. Whatever the nucleus, it is plausible that selective information processing is organized via different sectors of the RN.

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